Clinical Review

Review of Acute Severe Asthma

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Status asthmaticus in the 1980s is still occasionally a fatal disorder. Preventable causes appear to be common: failing to appreciate the severity of the illness and undertreatment, particularly with steroids. Thus, an objective data base, early treatment, and frequent reassessment are of paramount importance. Despite intensive therapeutic intervention, mechanical ventilation may be required. In managing the ventilator in these patients, efforts should be directed at minimizing peak airway pressures while vigorous conventional modalities are continued. The need to use mechanical ventilation does not imply that the course of the disease will worsen, and the long-term outlook generally is good. Thus, even a low mortality rate is troubling. Once the acute process has resolved, educating the patient and close follow-up are essential.

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Affecting 3% of the United States population, asthma is one of the most common chronic illnesses seen by clinicians.[1] Unfortunately, despite advances in the understanding of its pathophysiology and major advances in its therapy, this disease still constitutes a source of serious morbidity and death. Because asthma is a reversible process, generally with a good long-term prognosis, even a low mortality should be viewed as preventable. I describe the clinical characteristics of severe asthma and review conventional therapeutic modalities as well as management options for patients with refractory bronchospasm.

Mortality

A great deal has been written recently expressing concern over continuing fatalities due to acute severe asthma.[2-9] In Great Britain the rate of asthma-related deaths throughout the first part of the 20th century was stable until the 1960s when mortality inexplicably rose.[5] Rates have returned to baseline, but substantial mortality remains. New Zealand likewise has experienced an increase in the number of deaths due to asthma.[7] This increased number of asthma-related deaths was initially felt to be due to marketing and prescribing practices of β-agonist inhalers. There was concern that through a synergistic action with theophylline, the toxicity of these drugs was dramatically increased.[7,10] This does not explain, however, why mortality rates remain regional even though there are no longer important differences in drug availability worldwide. The results of a detailed assessment of various causes of asthma-related deaths suggest that avoidable factors are common.[4,10] Chief among these factors is an inability of patients or physicians to recognize the warning signs of an impending crisis due to severe asthma. It then becomes of great importance to stress the evaluation of a case of acute asthma so an optimal course of treatment can be mapped out.

Pathophysiology

Several factors contribute to the pronounced obstruction to airflow that is characteristic of severe asthma. The easily reversible bronchoconstriction of a mild asthma attack is associated with only a mild inflammatory reaction. With increasing severity, vasodilation leads to substantial bronchial mucosal edema. Submucosal tissues are also edematous, with engorged vessels and hypertrophied glands. The inflammatory process is marked by increased eosinophils—and, to a lesser extent, neutrophils—in the airways and bronchial walls along with increased mucous secretion. This process leads to plugging of the distal bronchioles with a thick gelatinous material.[11] At autopsy the lungs are uniformly hyperinflated and fail to collapse. With this extensive plugging, a patient's life is at greater risk because further bronchoconstriction can lead to complete airways obstruction. Physiologically as a consequence of this severe plugging, there is increased wasted ventilation, an increase in ventilation-perfusion mismatching, and an increase in the work of breathing. These processes eventually lead to hypoxemia, accompanied in the end by both a respiratory and a metabolic acidosis.[12]

Assessment

An accurate assessment of the severity of an asthmatic episode is crucial. Acute attacks account for nearly 1 million emergency department visits per year, most of which are treated on an outpatient basis.[13] As a consequence, a physician may become complacent and unattuned to the warning signs that would earmark a patient for admission. Attempts have been made to create an index that would identify more severely ill patients.[14] The use of such indices has not been widely adopted as prospective studies have failed to confirm their predictive accuracy.[15,16] Individualized objective and, to a lesser extent, subjective assessments are essential in determining the need for closer observation and more aggressive treatment.

Historically the most common complaint will be dyspnea. In contrast to the classic teaching, this more often is inspiratory rather than expiratory dyspnea.[17] Patients apparently are better than examining physicians, regardless of experience, at judging the severity of an asthma attack. Furthermore,

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ABBREVIATIONS USED IN TEXT

FEV_1 = forced expiratory volume in one second
PEEP = positive end-expiratory pressure

patients are fairly consistent in correlating subjective feelings of improvement with objectively measured values.[18] Conversely, a patient's estimate that his or her condition is worsening, especially after emergency department treatment, is a good indication for admission to hospital. Other key historical points that place patients in a higher risk group include present or previous steroid requirements, a previous hospital admission, previous intensive care treatment, and a history of mechanical ventilation for an asthmatic exacerbation. The failure of an outpatient treatment regimen that had previously been effective identifies a subgroup of patients with a greater degree of inflammation and plugging of the airways. Finally, patients with a gradual course of deterioration will generally be slower to respond to initial bronchodilator therapy.[19]

Several features of the physical examination can call attention to the severity of an attack, the seriousness of which may otherwise be overlooked. Tachycardia, with a heart rate of greater than 130 beats per minute, has been correlated with a forced expiratory volume in one second (FEV_1) of less than a liter. As the obstruction resolves, the pulse drops despite a continued use of sympathomimetics.[20] With severe obstruction, wide fluctuations in intrathoracic pressures throughout the respiratory cycle lead to pulsus paradoxus—an inspiratory drop in the systolic blood pressure of greater than 12 mm of mercury. Although a pulsus paradoxus may be absent in a case of severe obstruction, its presence correlates with an FEV_1 of less than 40% of predicted.[21,22] Although wheezing is considered a hallmark of asthma, its severity may not correlate with the severity of the attack. A "quiet chest" may portend a worsening ability to move air and thus can be an ominous sign.

The early clinical signs of fatiguing respiratory muscles include an increasing respiratory rate, respiratory alternans (alternation between abdominal and rib-cage breathing), and abdominal paradoxic breathing (a paradoxic inward motion during inspiration). Respiratory muscle fatigue occurs because of a progressive pathophysiologic course of events. Premature closure of narrowed airways during expiration leads to an increase in the end-expiratory lung volume. With hyperinflation, all of the inspiratory muscles are shorter than they should be at the start of inspiration. As a result, these muscles operate at a less than optimal segment of their force-length curve and more work is required to achieve a given level of ventilation.[23(p136)] As expected, a patient's sense of dyspnea increases proportionately to the increase in the respiratory muscle workload.[24] Respiratory muscle fatigue ensues with the development of tachypnea, discordant respiratory movements signaling an impending increase in the partial carbon dioxide pressure and overt respiratory failure.[25]

Although, as previously mentioned, patients are often able to estimate the degree of obstruction, it has also been found that some are more breathless than others for any given reduction in the FEV_1. This variation in breathlessness is maintained over a wide range of reductions in the FEV_1.[26] With this potential for error on the part of both patients and physicians, simple objective measurements are necessary and should be considered an extension of the physical examination during both the initial assessment and when quantitating a patient's response to therapy. To accomplish this, the FEV_1 and peak expiratory flow rate are most commonly used. Of these two, the peak expiratory flow rate is easier to determine because it requires only a short forced expiration similar to a cough after full inspiration. Severe obstruction is clearly present if the peak expiratory flow rate is less than 100 liters per minute before treatment or is less than 300 liters per minute after the initial treatment. The FEV_1 may be more difficult to measure in an acutely dyspneic patient. When obtainable, however, it is clear that an initial FEV_1 of less than 0.7 liters or a posttreatment value of less than 2.1 liters shows a need for aggressive therapy.[20]

Arterial blood gas measurements are useful in further quantifying the severity of an acute attack. The most commonly seen pattern in asthma of moderate severity is hypoxemia associated with respiratory alkalosis. Increased ventilatory drive arises primarily from increased afferent activity from the respiratory muscles in their struggle against the mechanical workload and from pulmonary irritant receptors of the vagus nerve.[24] As bronchospasm worsens, increasing the minute ventilation only results in small increases in alveolar ventilation. Because a hyperventilating person with asthma generally has a low P_{CO_2}, any P_{CO_2} of 40 mm of mercury or greater should be viewed with increasing concern. Once the FEV_1 drops below 25% of predicted, hypercapnia develops. Similarly but less consistently, there is a rough correlation between the partial arterial oxygen pressure and FEV_1, with hypoxemia substantially worsening when the FEV_1 falls below 40% of the predicted normal.[27]

During a severe asthma attack, a chest radiograph will show signs of hyperinflation—increased radiolucency, depressed diaphragms, and widened rib spaces—in as much as 55% of patients.[22] Less commonly, other abnormalities, such as pneumonia, pneumomediastinum, pneumothorax, or atelectasis from mucous plugging, may show a need for specific therapeutic intervention.[28]

The electrocardiogram in patients with severe acute asthma commonly shows a number of abnormalities including cor pulmonale, right ventricular strain, and right axis deviation. These changes have been correlated with the severity of the obstruction and alterations in the heart position due to hyperinflation.[29] The abnormalities usually lessen with bronchodilators and should not by themselves be considered a contraindication to sympathomimetic therapy.[22] Older patients, however, especially those with a history of heart disease, should be monitored to detect dysrhythmias.

Individually none of the aforementioned components of the history and physical examination are adequate for an accurate assessment. They must be taken in combination and then frequently reassessed. Failure to do so has been implicated as a preventable cause of death in patients with severe asthma.[4,6] With a complete data base, a rational treatment program can be started.

Initial Therapy

Pharmaceutical Measures

Several drugs are important for treating a severe asthma attack. The mechanisms of action of these medicines have been reviewed in great detail.[30-32] How these agents are used in a patient with an acute attack is highly variable and guided in large part by personal preference.

A classic approach is initially to administer a subcutaneous sympathomimetic, such as epinephrine or terbutaline sulfate, which is repeated if necessary. If satisfactory improvement is not achieved, intravenous aminophylline and an inhaled β-agonist, such as 0.3 ml metaproterenol sulfate, are administered, often concomitantly with steroids. If deterioration continues, a cholinergic agent such as atropine sulfate is given.

Although this regimen generally works reasonably well, recent data suggest that significant changes should be made in our initial approach to severe asthma. Fanta and coworkers have shown a notably better response to inhaled β-agonists than to subcutaneous epinephrine when given initially to a patient with severe obstruction.[33] Adding intravenous aminophylline to inhaled β-agonist therapy did not produce substantial improvement over the administration of the β-agonist alone. This finding supports those of previous studies showing a lack of added efficacy associated with an increased toxicity with the addition of aminophylline in the therapy for acute attacks.[10,34]

Although patients with asthma have been found to be less responsive to cholinergics than patients with chronic obstructive pulmonary disease,[35] combining nebulized ipratropium bromide with a sympathomimetic has been shown to be more efficacious than using either drug alone.[36] Furthermore, this can be done without clinically significant increases in side effects.[37,38] When it becomes available in the near future, nebulized ipratropium bromide, in combination with an inhaled β-agonist, may further improve our therapeutic approach to acutely ill persons with asthma.

Treating acute severe asthma with the use of corticosteroids is essential when patients do not respond readily to initial therapy. Several authors have suggested that an underuse of steroids has been a contributing factor in asthma mortality.[4,6,39,40] Statistically significant improvement usually occurs within an hour after administering the drug, with a peak effect occurring within seven to nine hours. As improvement may not be shown for as long as 36 hours in certain patients, it is best to initiate steroid therapy early.[13] Although the efficacy of the short-term use of corticosteroids has been shown,[41] recommendations for appropriate dosing have varied widely.[3,13,20,42,43] A study by Haskell and associates showed a significantly better response in the FEV_1 to the administration of high doses of methylprednisolone sodium succinate—125 mg given intravenously every six hours—than to low doses—either 15 mg or 40 mg given intravenously every six hours—with minimal side effects.[44] Once an acute process has subsided, the regimen can be converted to prednisone, 60 mg, and then tapered. The time of taper varies, however, with the cause and severity of the attack and must be tailored to each patient.

Supportive Measures

All severely ill asthmatic patients should be placed on oxygen therapy. Ventilation-perfusion alterations associated with severe obstruction commonly lead to hypoxemia.[27] Treatment with bronchodilators can transiently worsen the hypoxemia by a few millimeters of mercury by aggravating the $\dot{V}/\dot{Q}$ mismatching.[45] The hypoxemia is usually corrected using relatively low concentrations unless severe mucous impaction and secondary atelectasis are present. Oxygen flow rates should be guided by serial measurements of arterial blood gases.

Because of high insensible losses, dehydration is common. Fluid management is guided by principles used in other acutely ill patients. Greater caution—and at times invasive hemodynamic monitoring—is, of course, required with concomitant cardiovascular disease. If a patient requires mechanical ventilation, hypovolemia becomes even more dangerous because high inflation pressures cause a considerable decrease in venous return with subsequent hypotension.[46] Conversely, hypervolemia has never been shown to improve the clearance of pulmonary secretions and should also be avoided.[12,47]

The upper respiratory tract infections frequently associated with asthmatic flare-ups are more commonly viral than bacterial, so the routine use of antimicrobials in patients with acute asthma is to be discouraged.[48] Their administration is reserved for situations in which a combination of findings suggests a bacterial process—that is, an infiltrate on chest x-ray film, purulent sputum with bacteria on a Gram's stain, and leukocytosis.

Mechanical Ventilation

Despite extraordinary therapeutic efforts, a few patients will deteriorate so that mechanical ventilation becomes necessary. Various criteria for the need for intubation have been suggested,[49] but the decision must be tailored to individual cases. Often there is a fine line between giving the medication time to reach its maximal effect and continued deterioration so that intubation is done under less than optimal emergency conditions. Changes in mental state, however, and respiratory muscle fatigue with worsening respiratory acidosis generally indicate an inescapable need for mechanical ventilation. Although at times tempting, the use of sedatives must be avoided as these agents are a common iatrogenic cause of respiratory depression in already borderline patients.

Once the decision to intubate has been made, a nasotracheal approach is best after an adequate local application of lidocaine hydrochloride to the nasopharynx and larynx. This decreases patient discomfort and inhibits bronchospasm induced by irritating the larynx. This reflex, which is parasympathetically mediated, may be further inhibited with the administration of atropine.[12] A tube 8 mm or larger will minimize resistance and allow for more effective suctioning. Furthermore, if necessary, bronchoscopy may be more easily done through the larger tube.

After the airway has been secured, sedation with intravenous diazepam or morphine sulfate is needed. Although of questionable clinical significance,[11,47] morphine's potential to provoke histamine release is thought by many authors to make diazepam the drug of choice.[46,49,50]

Mechanically ventilated patients with asthma have an associated mortality rate of about 15%.[49] Complications in these patients occur at nearly three times the rate of those in patients ventilated for other reasons. This increase in morbidity and mortality is related to anoxic encephalopathy, cardiopulmonary failure, or pulmonary barotrauma as a result of extremely high pressures needed to overcome airway obstruction.[40,51,52]

Few clinical situations present as great a challenge to clinicians as mechanically ventilating an asthmatic patient. Several points may prove useful in the management of the ventilator. A volume-cycled ventilator should be used so that constant tidal volumes are maintained. Tidal volumes of 10 to

12 ml per kg body weight are delivered at a low ventilatory rate—that is, 8 to 12 breaths per minute. Caution is needed in adjusting the inspiratory-expiratory ratio. The increased expiratory time needed to prevent additional air trapping requires shortening the inspiratory time and using a higher inspiratory flow rate. Unfortunately, this increases peak airway pressures further. Sedation—and occasionally paralysis with pancuronium bromide—may be necessary to produce apnea. This allows for both a slower inspiratory flow and a longer expiratory time, which should aid in combating the high peak pressures and air trapping.[12] A paralyzed patient must be kept unaware by adequate sedation. Once a day the paralyzing medication should be stopped and consciousness restored so neurologic function can be assessed.

In an effort to minimize barotrauma, several authors suggest limiting peak inspiratory pressures to 50 to 55 cm of water.[51,53] If these levels are exceeded, adjustments in the tidal volume or inspiratory flow rate are made to lower the peak pressures. This may result in an inadequate minute volume with subsequent hypercapnia and respiratory acidosis. An elevated P_{CO_2} is accepted while the pH is corrected with an intravenous bicarbonate infusion. Critics of this approach point out the potential risk of posthypercapnic metabolic alkalosis.[49] Furthermore, the difference in central nervous system permeability between carbon dioxide and bicarbonate might result in continued central nervous system acidosis when the systemic pH was normal. This theoretically could produce alterations in the mental state.[53] Nevertheless, this combined strategy has been successful in lowering morbidity and mortality.[51]

The period of mechanical ventilation is usually brief, with an average duration of 61 hours.[47] During this time intense drug therapy is continued. Weaning cannot start until the airways obstruction has been adequately treated. This can be judged by a decrease in peak inspiratory pressures, a spontaneous negative inspiratory force of −30 cm of water, and a vital capacity of at least 15 ml per kg body weight.[12] In rare cases, the patient remains refractory despite conventional pharmaceutical therapy and mechanical ventilation. Under such circumstances, several other modalities can be considered.

Halothane

The general anesthetic halothane is a potent bronchodilator that neither stimulates respiratory secretions nor causes laryngeal irritation.[54] Despite halothane's potential benefits in asthmatic patients, its use is limited by side effects. Halothane readily produces circulatory depression, frequently with various arrhythmias because it is a strong negative inotrope.[55(p278)] Because of its narrow margin of safety, continuous bedside monitoring by an anesthesiologist is mandatory.

Bronchoscopy

As previously discussed, widespread tenacious plugging of the airways is an important feature in patients who die in status asthmaticus. Gross atelectasis, a common complication in these patients, may be caused by proximal mucous impactions. Removal of these plugs by fiber-optic bronchoscopy may improve ventilation.[13,52] There are anecdotal reports of successful bronchial lavage—generally with solutions that include acetylcysteine—to remove peripheral mucous plugging.[56-58] This procedure must be monitored closely, however, as it can initially worsen the patient's condition. Bronchoscopy has been associated with an increase in bronchospasm, an excess of respiratory tract infections, arrhythmias, and possibly pneumothorax.[39,59] In a deteriorating patient unable to tolerate bronchial lavage, extracorporeal membrane oxygenation support has been used to provide temporary support while serial bronchoscopies were successfully carried out.[59]

Positive End-Expiratory Pressure

The use of positive end-expiratory pressure (PEEP) has generally been considered to be contraindicated in asthma. It has been thought that PEEP increases an already high functional residual capacity and peak inflation pressures. However, high levels of PEEP have been reported to actually decrease peak airway pressures by "treating" the severe bronchospasm, with a subsequent improvement in patient status.[60]

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